EXHIBIT A

Declaration under 37 C.F.R. § 1.132 filed February 5, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Strong, Peter
U.S. Appln. No.	:	10/779,456
U.S. Filing Date	:	February 13, 2004
Title of Invention	:	CHITIN MICROPARTICLES AND THEIR MEDICAL USES
Confirm No.	:	9496
Examiner	:	Kim, Yunsoo
Art Unit	:	1644

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ON FEBRUARY 5, 2008

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Peter Strong, declare and state that:

1. I make this declaration in connection with U.S. application Serial No. 10/779,456. I am familiar with its prosecution history, particularly the Office Action mailed on October 5, 2007, as it pertains to the rejection under 35 U.S.C. §103(a) of claims 1-3, 5, 8, 9, 28-33, 35, and 36 as allegedly being unpatentable over Shibata *et al.* (J Immunol 164: 1314-21, 2000; hereinafter "Shibata") in view of Clinical Report (Pediatrics 100: 143-152, 1997) as evidenced by the specification of the present application, the Sigma Chitin powder product sheet, WO 97/20576 (hereinafter "the '576 publication"), Kim *et al.* (J Dent Child 71: 126-130, 2004; hereinafter "Kim"), and U.S. Patent No. 6,080,762 (hereinafter "the '762 patent").

2. I am a citizen of Great Britain. As indicated on my attached *Curriculum vitae*, I obtained a doctorate degree in Immunology from the University of Oxford and have been involved in a number of research areas, particularly related to allergies. I have served as the Chief Scientific

Officer and Director of CMP Therapeutics LTD., the assignee of this application, since 2004. In view of my education and experience, I consider myself to be an expert in the field to which this application pertains.

3. The claimed invention relates to a method of treating seasonal respiratory allergies, allergies to aeroallergens, or asthma in a patient comprising administering a therapeutically effective amount of a chitin microparticle (CMP) preparation intranasally or by inhalation to a patient in a therapeutically effective amount of between 0.01 and 100mg of CMP per kg of body weight. The CMPs have an average diameter of less than 10μm. According to the Examiner, Shibata relates to a method of treating an allergy caused by an aeroallergen such as ragweed, such that this method comprises administering CMP (N-acetyl-D-glucosamine) in saline (*e.g.*, a buffer). Shibata allegedly demonstrates that chitin administration provides prophylactic effects, causes ragweed desensitization, and induces Th1 cytokines which down regulate allergic airway inflammation. The Examiner relies on Clinical Report to allegedly show that nasal/intranasal administration is a well recognized route of delivering drugs in allergy treatment, and uses the specification of the present application and WO 97/20576 to allegedly show that insoluble chitosan is available for nasal administration. Further, the Examiner contends that the oral delivery dose of Shibata cannot be considered as a standard dose for intranasal delivery, uses the '762 patent to allegedly demonstrate that nasal or lung delivery has higher bioavailability as compared to oral delivery, and relies on Kim to show that a single oral dose of 0.7mg/kg is equivalent to an intranasal dose of 0.3mg/kg.

4. Contrary to the Examiner's assertion, one of ordinary skill in the art would not recognize that Shibata relates to a method of treating seasonal respiratory allergies, allergies to aeroallergens, or asthma. In Shibata, the mice used to test the CMP compositions were initially sensitized by intraperitoneal (i.p.) injection of ragweed allergen (see page 1315, left column). The purpose of the initial injections was to induce the allergy. The subsequent challenge to the mice was by intratracheal (i.t.) introduction of further ragweed allergen, which involves making a slit in the trachea and instilling allergen into the lungs – but notably **not** the upper respiratory tract or nasal passages – of the mouse. Hence, the challenge by i.t. introduction in Shibata only instills the lungs, although diseases like allergic rhinitis and asthma involve the upper respiratory tract as well as the lungs. Allergens do not bypass the upper tract as in Shibata's experiments. In fact, there is no indication in Shibata that orally administered CMP actually treats asthma, and at

most Shibata speculates that "oral administration of chitin may be a substitute for [such] bacterial exposure" (page 1320, right column).

5. In addition, the CMP composition in Shibata is administered orally and is not coupled or added to the initial i.p sensitization. The assumption in Shibata is that gut macrophages which contact the CMP migrate to the lungs of the mice, although there is no direct evidence in Shibata that substantiates this premise. Thus, all that is demonstrated in Shibata is that orally administered CMP down-regulates serum IgE and lung eosinophilia.

6. In contrast, the Examples in the application and the experiments described herein directly show that delivery of CMP by the claimed routes can treat seasonal respiratory allergies, allergies to aeroallergens, or asthma. Unlike in Shibata, these studies are more realistic since they involve stimulation of the entire nasal-pulmonary mucosa. For instance, the present application demonstrates that intranasal application of CMP was effective in down-regulating classic clinical physiological symptoms of allergic disease as measured by changes in airway hyper-responsiveness as well as indirect measurements such as serum IgE (see Example 5) and peripheral blood eosinophilia (see Example 1 and 2). This study used microgram quantities of CMP prepared by sonication of crab shell purified chitin powder obtained from Sigma Chemical Co. Analysis of the CMP revealed that the particles have a mean diameter of in the range of submicron up to 50μm, with 98% < 20μm. The application of CMP also induced an up-regulation of IL-12 and IFNγ, which are Th1-type cytokines with known anti-allergic effects, and a down-regulation of IL-4, which is one of the most potent Th2 cytokines in allergic disease (see Example 14). Treatment with CMP also inhibited the development of asthma in mice as indicated by a significant attenuation in airway hyperresponsiveness (see Example 12) which is a direct clinical assessment of allergic disease of the airways as prominent in asthma.

7. Furthermore, additional studies were conducted to test the efficacy of intranasally applied CMP as claimed against allergic disease induced by a broad range of clinically important aeroallergens including house dust mite, grass pollens, tree pollens, ragweed pollen as well as cat and dog dander allergens. The effect of treatment was assessed by whole body plethysmography to give a direct physiological measure of the asthmatic status of the lungs. In this technique, a transducer measures fluctuations in air pressure which is converted into a parameter called enhanced pause (Penh). Measurements are expressed as the % increase over baseline value.

Controls usually show an elevation of <100% above baseline, while asthmatic shows Penh that is >150% and severely asthmatic have Penh >200%.

8. In this study, mice were sensitized by i.p. injection of allergen extract in alum over 4 weeks. Mice were then challenged with allergen extract administered intranasally, and treated with a dose of 20-50μg (0.8mg/kg body weight) of CMP administered intranasally either 1-2 hours before or after allergen challenge. This challenge / treatment protocol was continued for a number of days until an asthmatic response was observed.

9. Intranasal Treatment with 20μg doses of CMP effectively abolished the development of asthmatic airway hyperresponsiveness induced by repeated allergen challenge with Bermuda grass pollen (see FIG. 1; P<0.0005) and Timothy grass pollen (see FIG. 2; P<0.01).

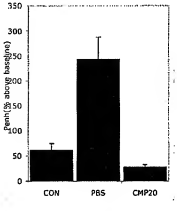

Figure 1

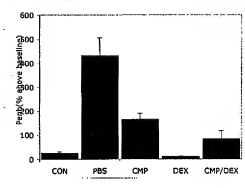

Figure 2

10. A group of allergic mice were also treated by injections of the corticosteroid dexamethasone (DEX) at an equivalent body weight dose used in humans. Intranasal Administration of CMP as claimed was as effective as the steroid drug in preventing asthma induced by Timothy grass pollen and suggests that the methods of the invention are capable of preventing the development of pulmonary allergic disease. When CMP-intranasally treated mice were given a large allergen challenge by Timothy grass pollen 24 hours after the last intranasal treatment with CMP, mice that had been treated with 20μg intranasal doses of CMP or injection with dexamethasone showed a 50% reduction in the asthmatic response (FIG. 3.).

11. Intranasal Treatment with 20μg doses of CMP was highly effective (see FIG. 4; P<0.005) against ragweed-induced allergic disease and compared well to dexamethasone injections. Ragweed is the most important cause of allergic rhinitis in the US and Canada and approximately

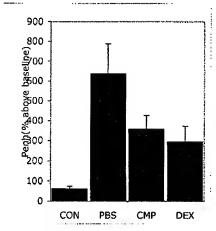

Figure 3.

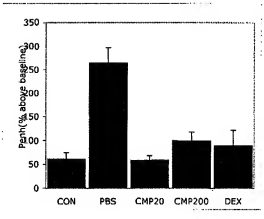

Figure 4.

75% of hay fever patients are allergic to ragweed. Comparison with a high dose treatment with 200μg of CMP given intranasally showed no significant advantage over the 20μg doses in reducing allergic airway hyper-responsiveness.

12. The methods of the present invention were tested against three common and important tree pollens: cedar pollen, birch pollen and oak pollen. Allergy to tree pollens accounts for about 30% of hay fever cases and one in four sufferers have allergies to both grass and tree pollens. Birch pollen seems to contain some of the most potent allergens such as Bet v 1 and in Europe more than 96% of tree pollen allergic sufferers are allergic to birch pollen. In Japan, allergy to cedar tree pollen is a public health issue affecting up to 20% of the population.

13. Intranasal Treatment with 20μg doses of CMP as claimed provided significant protection against development of airway hyperresponsiveness induced by cedar pollen (FIG. 5; P<0.01) and birch pollen (FIG. 6; P<0.001). As for oak pollen, treatment with 40μg of CMP significantly protected against the development of asthma (FIG. 7; P<0.005) measured 24 hours after the allergen challenge.

14. The effects of intranasal treatment with CMP as claimed were also determined for cat and dog allergies. A treatment dose of 40μg (1.6mg/kg body weight) given intranasally was used. The CMP treatment reduced the onset of asthma provoked by the airway allergen challenge and was statistically very much lower on day 2 ($P<0.05$) and day 3 ($P<0.005$). Unlike treatment with

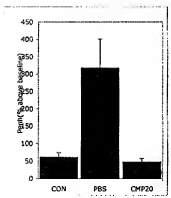

Figure 5

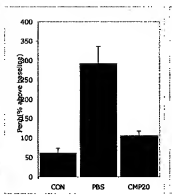

Figure 6

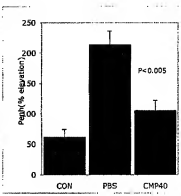

Figure 7

PBS saline, the intranasal CMP treatment seemed to progressively reduce the asthmatic status over time (FIG. 8).

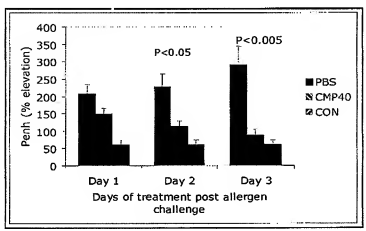

Figure 8

15. In the dog allergy study, mice were first made asthmatic by i.n. allergen challenge and then rested for 12 days before a further allergen challenge with or without treatment with 50μg CMP. Plethysmography was measured 24 hours later and revealed that intranasal CMP treatment as claimed reduced airway hyperresponsiveness by 32% and almost reached significance (FIG. 9; P=0.058).

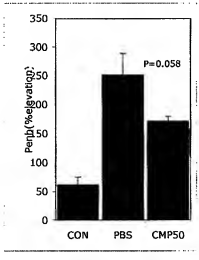

Figure 9

16. Together, these results demonstrate that the intranasal application of CMP as claimed is an effective prophylactic treatment for reducing the symptoms of allergic asthma produced in response to a broad range of common aeroallergens, including house dustmite, grass pollens, tree pollens, ragweed and animal dander. Importantly, Shibata does not show this and only implies that stimulation of Th1 cytokines by CMP would be beneficial for allergy, but the only direct physiological evidence provided is lung histology. Based upon Shibata's limited results, one skilled in the art would not presume that the methods of Shibata treat allergies as recited in the instant claims. Further, the skilled artisan would recognize that Clinical Reports does remedy the deficiencies in Shibata.

17. In addition, one skilled in the art would not apply the secondary references in support of the combination of Shibata and Clinical Reports. The secondary references relate to

"normal" types of drugs that are soluble and delivered systemically to the patient. Nasal delivery is useful for many drugs simply because the mucosa is thin and well-supplied with blood vessels. It is therefore a route that is sometimes useful for administering soluble drugs designed for systemic delivery to a site where the drugs are likely to be absorbed well via the blood vessels in the nose. This assertion is supported by the secondary references; for example, Kim relates to midazolam, which is a water-soluble drug, and indicates that intranasal delivery of midazolam has the potential advantage of rapid absorption (see page 126, left column). Also, the '762 patent relates to Raloxifene which is shown to be a soluble drug by the very fact that the efficacy of the delivery of Raloxifene was determined in the examples by measuring its concentration in blood samples from monkeys (column 7, lines 1-9) and by the explanation of the mechanism of intranasal delivery for soluble, systemically delivered drugs (column 7, lines 47-64).

18. In contrast to these normal drugs, CMP is not soluble, as indicated in the present specification (paragraph bridging pages 11 and 12) and in Shibata (page 1314, right column). The present invention also does not attempt to deliver CMP systemically, but to restrict it to the mucosa of the nose and upper respiratory tract where it acts topically, not systemically, improving immune function in these passages. Therefore, one skilled in the art would not apply the teachings of the secondary references to support the combination of Shibata and Clinical Reports.

19. Finally, one skilled in the art would consider the advantages of the present invention, which are not considered by the cited references. Firstly, the CMP composition of the present invention is formulated for delivery as a nasal spray, such that its immune modulating properties can be specifically directed to the site of allergic inflammation. As a result, the composition is much more effective for treating diseases of the nasal passages such as allergic rhinitis. Notably, there is no evidence from Shibata or Clinical Reports that indicates that oral delivery is effective for these conditions.

20. Also, there are safety advantages in using the claimed delivery routes of the present invention as compared to Shibata and Clinical Reports. If CMP produced an adverse reaction as it might in someone allergic to shrimp (generally used as a source of the CMP), then removing it after oral administration as used in Shibata and Clinical Reports would not be easy compared to nasal application, where the CMP could be removed by sneezing and irrigation.

21. Moreover, the present invention demonstrates greater efficiency of effect as compared to Shibata and Clinical Reports. Even assuming that the orally delivered CMP in Shibata did activate macrophages in the GI tract and a tiny fraction of these migrated to the nasal mucosa, the process would be inefficient as compared to the claimed routes of administration. In particular, in the absence of continual stimulation by proximity to CMP particles, the level of activation could not be maintained and the immune modulating effect in the nose would be short lived. Delivering CMP nasally ensures more robust and sustained activation of resident macrophages. It is clearly a more efficient process of activating nasal macrophages, which can then down-regulate asthma or allergic rhinitis. There is also concern of how the efficiency of the oral routes discussed in Shibata since nasal resident macrophages are more specialized for the nose and controlling immune status in the nasal mucosa, just as gut macrophages are specialized for immune status in the gut. Shibata and Clinical Reports do not even consider that oral routes would be less efficient for activating specific resident nasal macrophages as compared to intransal routes.

22. In summary, the arguments presented herein demonstrate that one skilled in the art would not recognize that the present invention is obvious in view of the present invention. The skilled artisan would not consider that Shibata and Clinical Reports relates to a method of treating the allergies recited in the claims, nor would the skilled artisan consider that the teachings of the secondary references can be applied in support of Shibata and Clinical Reports. Further, one skilled in the art would recognize that the present invention has many advantages that are not considered or taught in the cited references. Therefore, I believe that the claimed invention is not obvious in consideration of the cited references.

23. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 1 February 2008 Peter Strong

Peter Strong